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EXAMINER	
WOODWARD, CHERIE MICHELLE	
ART UNIT	PAPER NUMBER
1647	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/23/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/527,975	LE BUANNEC ET AL.	
	Examiner	Art Unit	
	Cherie M. Woodward	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *11-20 and 26-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,21-25 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 March 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/9/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I (claims 1-23 and 25) and the species of TNFα and Keyhole Limpet Hemocyanin (KLH) in the reply filed on 20 October 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). The Examiner has determined that claim 24 may be properly rejoined with the elected group because the search results would likely overlap.

Formal Matters

2. Claims 1-29 are pending. Claims 11-20, and 26-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected inventions, there being no allowable generic or linking claim. Claims 1-10, 21-25, and 29 are under examination.

Specification - Objections

3. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

4. The use of numerous trademarks have been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology. (See, for example, LABRASOL p. 33, ALHYDRAGEL p. 33, SUPERFOS p. 33, COSTAR p. 41, TWEEN p. 41.)

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Objections

5. Claim 9 is objected to because of the following informalities: the word cytokines is misspelled. Appropriate correction is required.

6. Claim 10 objected to because of the following informalities: the claim recites a Markush Group where the members are "selected amongst..." the recited group. This is non-standard Markush language. Applicant is advised to refer to MPEP 2173.05(h) for examples of proper Markush group language.

Provisional Obvious-Type Double Patenting Rejection

7. Claims 1-10, 21-25, and 29 are provisionally rejected on the ground of nonstatutory double patenting over claims 26 and 27 of copending Application No. 11/135,660. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: the instant claims recite a stable immunogenic product comprising TNFα covalently linked to a carrier protein (KLH, as elected) where the chemical binding agent is glutaraldehyde. Claims 26 and 27 recite an immunogenic product comprising antigenic heterocomplexes of TNFα and a carrier protein and a vaccine composition comprising a stable immunogenic product comprising antigenic heterocomplexes of TNFα and a carrier protein and a pharmaceutically acceptable carrier.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim Rejections - 35 USC § 112, First Paragraph

Enablement

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-10, 21-25, and 29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability, 5) existence of working samples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims recite a stable immunogenic product for inducing antibodies raised against one or more antigenic proteins in a subject, characterized in that it comprises protein immunogenic heterocomplexes consisting of associations between (i) antigenic protein molecules and (ii) carrier protein molecules and in that less than 40% of the antigenic proteins (i) are covalently linked to carrier protein molecules (ii); an immunogenic product according to claim 1, characterized in that each heterocomplex comprise (i) a plurality of antigenic proteins linked to (ii) a carrier protein molecule; an immunogenic product according to claim 2, characterized in that, for each immunogenic heterocomplex, the plurality of antigenic proteins (i) is made up of a plurality of specimens of a single antigenic protein; an immunogenic product according to claim 2, characterized in that, for each immunogenic heterocomplex, the antigenic proteins (i) consist of a plurality of specimens of a protein being normally recognized as a self protein by the cells of said subject's immune system; a product according to claim 1, characterized in that it comprises 5 to 50 antigenic proteins (i) for one carrier protein molecule (ii), preferably 20 to 40 antigenic proteins (i) for one carrier protein molecule (ii); an immunogenic product according to claim 1,

characterized in that the covalent bonds between one or more antigenic proteins (i) and the carrier protein molecule (ii) are made through a bifunctional bond chemical agent; an immunogenic product according to claim 6, characterized in that said binding chemical agent comprises at least two free aldehyde functions; an immunogenic product according to claim 7, characterized in that said binding chemical agent is glutaraldehyde; an immunogenic product according to claim 1, characterized in that the antigenic protein(s) (i) consist(s) in cytokins naturally produced by said subject; an immunogenic product according to claim 9, characterized in that the antigenic protein(s) (i) is/are selected amongst interleukin-4, alpha interferon, gamma interferon, VEGF, interleukin-10, TNF alpha, TGF beta, interleukin-5 and interleukin-6; a composition comprising an immunogenic product according to claim 1; a pharmaceutical composition comprising an immunogenic product according to claim 1 in association with one or more physiologically compatible excipients; an immunogenic composition comprising an immunogenic product according to claim 1 in association with one or more physiologically compatible excipients; a vaccine composition comprising an immunogenic product according to claim 1 in association with one or more physiologically compatible excipients; an immunogenic composition or a vaccine composition according to claim 23, characterized in that it comprises the CpG immunity adjuvant; an immunogenic product according to claim 1, characterized in that it is selected amongst products comprising the following heterocomplexes, wherein the antigenic proteins (i), on the one hand, and the protein carrier molecule (ii), on the other hand, are respectively (i) TNFα and KLH.

The nature of the invention is drawn to an immunogenic composition and/or a vaccine against endogenous TNFα by complexing a TNFα protein with a carrier protein to form an immunogenic composition such that anti-TNFα antibodies would be made endogenously. The level of skill of those in the art is high due to the complex nature of vaccine production and the immune response to vaccines.

The state of the art discloses that antigen conjugation to a carrier protein is important because peptides are small molecules, that alone do not tend to be immunogenic, thus possibly eliciting a weak immune response (see, for example, Antigen Design and Sera Purification, Sigma Genosys, 2006). The state of the art also discloses TNFα molecules may be formulated as vaccines against TNFα with pharmaceutically acceptable adjuvants for the prevention of treatment of chronic inflammatory diseases (Jensen et al., WO 98/46642 (published 22 October 1998). The use of Keyhole Limpet Hemocyanin (KLH) as a peptide conjugate in vaccines is also well known (see, Musselli et al., J Cancer Res Clin Oncol. 2001 Oct: 127(Suppl 2):R20-R26). Procedures for preparing biologically inactive but immunogenic Tat toxoids for human use is also well known (see Le Buanec et al., Biomed & Pharmacother. 2000 Feb; 54:41-4). Le Buanec teach the use of gluteraldehyde, formaldehyde, EDTA,

and glycine in a method of preparing an immunogenic HIV-1 Tat protein vaccine for human use (pp. 41-42, see Reagents and Procedures of Tat inactivation). Zagury et al., (US Patent 6,455,045, 24 September 2002, benefit to June 27, 1994) and Zagury et al., (US Patent 6,093,405, 25 July 2000, benefit to 27 June 1994) disclose that cytokines, which are biologically inactive in humans, but remain immunogenic, are used in pharmaceutical compositions to promote a neutralizing immune response to native cytokines when administered to a subject to treat conditions and disorders associated with the overproduction of cytokines (see abstracts). Compositions comprising TNFα are taught at (column 1, line 53 of the '405 patent and column 1, line 60 of the '045 patent). Additionally, Zagury et al., (US Patent 7,002,482 4 April 2006, benefit to 15 June 1999) disclose the use and preparation of immunogenic compounds whose antigenic properties are inactivated by at least 70% through a physical and/or chemical treatment and preserving sufficient immunogenic properties for generating antibodies that neutralize or block the native protein (see abstract). Further, Zagury et al., (US Patent 7,878,370, 12 April 2005, benefit to 26 October 2001) disclose chemically modified murine TNFα and methods of producing a vaccine composition comprising a chemically modified TNFα for combating overproduction of native TNFα by carboxyamidination and use of EDTA (see Examples 4 and 5, column 6; Example 6, column 7; and Example 24, column 15).

The disclosure recites a preparation entitled KLH-murine TNFα heterocomplex in Example 9 (p. 38, line 10). However, the example itself teaches conjugating KLH to human IFNα rather than TNFα (p. 38, lines 14-27). The Examiner could not find where Applicant has taught how to make a KLH-murine TNFα heterocomplex or KLH-TNFα complex from any other species, at any place in the disclosure. There are no other examples or guidance in the specification teaching how to make the claimed immunogenic composition using KLH conjugated to TNFα.

Moreover, Applicant has not disclosed how to make a vaccine. In order to demonstrate the making of a vaccine, examples of its use as a shield against subsequent infection must be disclosed and guidance provided on how to make and use the vaccine. The disclosure teaches that only the humoral response in mice were measured after administration of a composition comprising KLH and murine TNFα (see p. 64, part of Example 32). No T-cell activation is shown anywhere in the disclosure such that it may be determined that cellular immunity was activated to induce memory effector cell responses to subsequent antigen presentation. As such, the specification, as originally filed, fails to provide enabling support for any vaccine composition.

Only murine TNFα proteins are mentioned in the disclosure. The claims, as written, do not limit the species from which TNFα proteins may be obtained or conjugated into a heterocomplex with a carrier

protein to make the claimed immunogenic product. Additionally, Applicant states that "obviously, depending on the preparations, the percentage of molecules of antigenic protein of interest covalently linked to the carrier protein molecules could significantly vary" (p. 12, lines 28-30). As such, Applicant provides no guidance whatsoever to teach one of skill in the art to produce or maintain a percentage of 40% of the antigenic protein as covalently linked to the carrier protein molecules. No guidance is provided such that a certain amount of formaldehyde or other conjugating agent may be used to produce and/or maintain such a percentage of covalently linked conjugate molecules. Applicant provides no disclosure or data reflective of kinetics such that one of skill may determine the on-off rates of covalent linkage in any given solution or buffer. In short, there is no support in the disclosure as originally filed that provides and guidance on how to make or use the composition requiring that less than 40% of the antigenic proteins be covalently linked to the carrier protein molecules, as claimed. Further, the term "less than 40% of the antigenic proteins" can mean no proteins are covalently linked to carrier protein molecules.

The specification fails to teach the skilled artisan how to make the claimed stable immunogenic products without resorting to undue experimentation to determine which components of the formulations, such as generic heterocomplexes of TNFα (as elected) and a carrier protein (such as KLH, as elected), or generic carrier proteins, can be combined within the breadth of the claimed ranges to produce an effective vaccine that will produce the desired results.

Example 32 (p. 63 of the disclosure) provides guidance on how to use the KLH-murine TNFα heterocomplex in mice. However, there is no guidance provided on how to use a KLH- TNFα heterocomplex in any other species.

The disclosure recites limited "carrier proteins" and only provides working examples of how to use murine TNFα-KLH conjugates, but not how to make them. Examples of other cytokine peptides are taught as being conjugated to the carrier protein, KLH. However, it would require undue experimentation to determine whether the full breadth of all carrier proteins, as claimed, would be functional in a vaccine composition. Additionally, Applicants' claims are excessively broad due, in part, to the complex and diverse nature of producing vaccines that produce an immune response, but not a toxic or lethal immune response. Applicant fails to teach how to make the claimed compositions comprising multiple generic antigenic proteins comprising protein immunogenic heterocomplexes consisting of associations between antigenic protein molecules and carrier protein molecules, or comprising TNFα conjugated to KLH (as elected), with the recited ratios or numbers of generic antigenic proteins.

Similarly, the claims recite, but the disclosure fails to teach generic bifunctional bond chemical agents, generic binding chemical agents comprising at least two free aldehyde functions, generic physiologically compatible excipients, or a generic CpG immunity adjuvant. It would require undue experimentation to make, test, and use the numerous unspecified bifunctional bond chemical agents, generic binding chemical agents comprising at least two free aldehyde functions, generic physiologically compatible excipients, and a generic CpG immunity adjuvant, to determine whether any of the aforementioned compositions would create a functional immunogenic product in any species.

Additionally, claim 25 recites an immunogenic composition or vaccine composition characterized in that it comprises the CpG immunity adjuvant. There is no disclosure nor any guidance whatsoever in the specification such that one may figure out what is meant by "CpG immunity adjuvant." Applicant has failed to discuss the CpG immunity adjuvant and has failed to teach how to utilize it to make or use the claimed compositions. The only place that the phrase "CpG immunity adjuvant" appears in the disclosure is in claim 25.

Therefore, based on the discussions above concerning the art's recognition that although TNFα molecules may be formulated as vaccines against TNFα with pharmaceutically acceptable adjuvants for the forming endogenous antibodies against TNFα, conjugation to specific carrier proteins are important because self-peptides such as TNFα may not be immunogenic alone, thus possibly eliciting a weak immune response. Additionally, the specification fails to teach the skilled artisan how to make the claimed stable immunogenic products without resorting to undue experimentation to determine which components of the formulations, such as the percentage of covalently linked antigenic protein to carrier protein, generic heterocomplexes of TNFα and a carrier protein, or generic carrier proteins themselves can be combined within the breadth of the claimed ranges to produce an effective immunogenic composition and/or vaccine.

Due to the large quantity of experimentation necessary to determine which carrier proteins to use to conjugate to generic antigenic proteins, or specifically conjugating KLH to TNFα (as elected), the lack of direction/guidance presented in the specification regarding same, the absence of sufficient working examples directed to same, the complex nature of the invention, the state of the prior art establishing that methods of producing vaccines are very specific in nature, and the breadth of the claims which fail to recite specific compounds or concentrations/amounts of compounds, undue experimentation would be required of the skilled artisan to make and/or use the invention as claimed.

Claim Rejections - 35 USC § 112, First Paragraph

Written Description

10. Claims 1-10, 21-25, and 29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The claims recite a stable immunogenic product for inducing antibodies raised against one or more antigenic proteins in a subject, characterized in that it comprises protein immunogenic heterocomplexes consisting of associations between (i) antigenic protein molecules and (ii) carrier protein molecules and in that less than 40% of the antigenic proteins (i) are covalently linked to carrier protein molecules (ii); an immunogenic product according to claim 1, characterized in that each heterocomplex comprise (i) a plurality of antigenic proteins linked to (ii) a carrier protein molecule; an immunogenic product according to claim 2, characterized in that, for each immunogenic heterocomplex, the plurality of antigenic proteins (i) is made up of a plurality of specimens of a single antigenic protein; an immunogenic product according to claim 2, characterized in that, for each immunogenic heterocomplex, the antigenic proteins (i) consist of a plurality of specimens of a protein being normally recognized as a self protein by the cells of said subject's immune system; a product according to claim 1, characterized in that it comprises 5 to 50 antigenic proteins (i) for one carrier protein molecule (ii), preferably 20 to 40 antigenic proteins (i) for one carrier protein molecule (ii); an immunogenic product according to claim 1, characterized in that the covalent bonds between one or more antigenic proteins (i) and the carrier protein molecule (ii) are made through a bifunctional bond chemical agent; an immunogenic product according to claim 6, characterized in that said binding chemical agent comprises at least two free aldehyde functions; an immunogenic product according to claim 7, characterized in that said binding chemical agent is glutaraldehyde; an immunogenic product according to claim 1, characterized in that the antigenic protein(s) (i) consist(s) in cytokins naturally produced by said subject; an immunogenic product according to claim 9, characterized in that the antigenic protein(s) (i) is/are selected amongst interleukin-4, alpha interferon, gamma interferon, VEGF, interleukin-10, TNF alpha, TGF beta, interleukin-5 and interleukin-6; a composition comprising an immunogenic product according to claim 1; a pharmaceutical

composition comprising an immunogenic product according to claim 1 in association with one or more physiologically compatible excipients; an immunogenic composition comprising an immunogenic product according to claim 1 in association with one or more physiologically compatible excipients; a vaccine composition comprising an immunogenic product according to claim 1 in association with one or more physiologically compatible excipients; an immunogenic composition or a vaccine composition according to claim 23, characterized in that it comprises the CpG immunity adjuvant; an immunogenic product according to claim 1, characterized in that it is selected amongst products comprising the following heterocomplexes, wherein the antigenic proteins (i), on the one hand, and the protein carrier molecule (ii), on the other hand, are respectively (i) TNFα and KLH.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117). A review of the language of the claim indicates that these claims are drawn to a genus, i.e., generic heterocomplexes of antigenic proteins and carrier proteins, of which less than 40% of the antigenic proteins are covalently linked to carrier protein molecules, non-species specific TNFα proteins complexed with generic carrier proteins, numerous unspecified antigenic proteins complexed to one carrier protein, generic bifunctional bond chemical agents, generic binding chemical agents comprising at least two free aldehyde functions, generic physiologically compatible excipients, a generic CpG immunity adjuvant, and a vaccine.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In *Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that, while applicants are not required to disclose every species encompassed by a genus, the description of the genus is achieved by the

recitation of a representative number of species falling within the scope of the claimed genus. At section B(1), the court states, "An adequate written description of a DNA ... requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention."

There is one species of immunogenic complex, as elected, that is within the scope of the claimed genus, *i.e.* a murine TNFα –KLH conjugate protein is recited in the disclosure. The disclosure of a single species may provide an adequate written description of a genus when the species disclosed is representative of the genus. However, the present claim encompasses numerous species that are not further described.

No adequate description is given regarding which members of the claimed genera of heterocomplexes of antigenic proteins and a carrier protein would be effective in the composition. Similarly, there is no adequate description in the disclosure as to which generic carrier proteins would be effective in the composition. Additionally, there are no descriptions anywhere in the disclosure of T-cell activation or memory effector cell responses that would indicate that any of Applicant's compositions were vaccines.

In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genus, which are generic heterocomplexes of antigenic proteins and carrier proteins, of which less than 40% of the antigenic proteins are covalently linked to carrier protein molecules, non-species specific TNFα proteins complexed with generic carrier proteins, numerous unspecified antigenic proteins complexed to one carrier protein, generic bifunctional bond chemical agents, generic binding chemical agents comprising at least two free aldehyde functions, generic physiologically compatible excipients, a generic CpG immunity adjuvant, and a vaccine. One of skill in the art would not recognize from the disclosure that the applicant was in possession of the genus. The specification does not clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed (see *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112, Second Paragraph

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 1-10, 21-25, and 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite a stable immunogenic product for inducing antibodies raised against one or more antigenic proteins in a subject, characterized in that it comprises protein immunogenic heterocomplexes consisting of associations between (i) antigenic protein molecules and (ii) carrier protein molecules and in that less than 40% of the antigenic proteins (i) are covalently linked to carrier protein molecules (ii). The term "less than 40% of the antigenic proteins" can mean no proteins are covalently linked to carrier protein molecules. The metes and bounds of the term "less than 40%" is indefinite. Claims 2-10, 12, 21-25, and 29 are rejected as being dependent on claim 1.

13. Claim 25 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 25 recites an immunogenic composition or a vaccine product characterized in that it comprises the CpG immunity adjuvant. The phrase "CpG immunity adjuvant" is not mentioned or disclosed in the specification such that the skilled artisan would understand what the Applicant meant. The term, as recited, is confusing, is not defined in the specification, and is not commonly used in the art.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 1-4, 9-10, 21-24, and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Wedlock et al., (Immunol and Cell Biology. 1999; 77:28-33).

The claims recite a stable immunogenic product for inducing antibodies raised against one or more antigenic proteins in a subject, characterized in that it comprises protein immunogenic heterocomplexes consisting of associations between (i) antigenic protein molecules and (ii) carrier protein molecules and in that less than 40% of the antigenic proteins (i) are covalently linked to carrier protein molecules (ii); an immunogenic product according to claim 1, characterized in that each heterocomplex comprise (i) a plurality of antigenic proteins linked to (ii) a carrier protein molecule; an immunogenic product according to claim 2, characterized in that, for each immunogenic heterocomplex, the plurality of

antigenic proteins (i) is made up of a plurality of specimens of a single antigenic protein; an immunogenic product according to claim 2, characterized in that, for each immunogenic heterocomplex, the antigenic proteins (i) consist of a plurality of specimens of a protein being normally recognized as a self protein by the cells of said subject's immune system; an immunogenic product according to claim 1, characterized in that the antigenic protein(s) (i) consist(s) in cytokins naturally produced by said subject; an immunogenic product according to claim 9, characterized in that the antigenic protein(s) (i) is/are selected amongst TNF alpha (as elected); an immunogenic product according to claim 1, characterized in that the antigenic protein(s) is/are selected amongst proteins lethal to man at a doses lower than 1 mg; a composition comprising an immunogenic product according to claim 1; a pharmaceutical composition comprising an immunogenic product according to claim 1 in association with one or more physiologically compatible excipients; an immunogenic composition comprising an immunogenic product according to claim 1 in association with one or more physiologically compatible excipients; a vaccine composition comprising an immunogenic product according to claim 1 in association with one or more physiologically compatible excipients; an immunogenic product according to claim 1, characterized in that it is selected amongst products comprising the following heterocomplexes, wherein the antigenic proteins (i), on the one hand, and the protein carrier molecule (ii), on the other hand, are respectively (i) TNFα and KLH.

Wedlock et al., teach an immunogenic composition comprising KLH and brushtail possum-TNFα in a PBS buffer (see entire reference, especially, p.31, first column, paragraph 1).

16. Claims 1-4, 6-10, 21-25, and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Zagury et al., (WO 02/011759 A1, published 2 February 2002, in French. The certified English translation of which found in US 2004/0028647 A1, the US patent application filing under 35 USC 371 PCT/FR01/02575).

The claims recite a stable immunogenic product for inducing antibodies raised against one or more antigenic proteins in a subject, characterized in that it comprises protein immunogenic heterocomplexes consisting of associations between (i) antigenic protein molecules and (ii) carrier protein molecules and in that less than 40% of the antigenic proteins (i) are covalently linked to carrier protein molecules (ii); an immunogenic product according to claim 1, characterized in that each heterocomplex comprise (i) a plurality of antigenic proteins linked to (ii) a carrier protein molecule; an immunogenic product according to claim 2, characterized in that, for each immunogenic heterocomplex, the plurality of antigenic proteins (i) is made up of a plurality of specimens of a single antigenic protein; an immunogenic product according to claim 2, characterized in that, for each immunogenic heterocomplex, the antigenic

proteins (i) consist of a plurality of specimens of a protein being normally recognized as a self protein by the cells of said subject's immune system; an immunogenic product according to claim 1, characterized in that the covalent bonds between one or more antigenic proteins (i) and the carrier protein molecule (ii) are made through a bifunctional bond chemical agent; an immunogenic product according to claim 6, characterized in that said binding chemical agent comprises at least two free aldehyde functions; an immunogenic product according to claim 7, characterized in that said binding chemical agent is glutaraldehyde; an immunogenic product according to claim 1, characterized in that the antigenic protein(s) (i) consist(s) in cytokins naturally produced by said subject; an immunogenic product according to claim 9, characterized in that the antigenic protein(s) (i) is/are selected amongst TNF alpha (as elected); a composition comprising an immunogenic product according to claim 1; a pharmaceutical composition comprising an immunogenic product according to claim 1 in association with one or more physiologically compatible excipients; an immunogenic composition comprising an immunogenic product according to claim 1 in association with one or more physiologically compatible excipients; a vaccine composition comprising an immunogenic product according to claim 1 in association with one or more physiologically compatible excipients; an immunogenic product according to claim 1, characterized in that it is selected amongst products comprising the following heterocomplexes, wherein the antigenic proteins (i), on the one hand, and the protein carrier molecule (ii), on the other hand, are respectively (i) TNFα and KLH.

Zagury et al., teach immunogenic compositions with an anti-cytokine effect comprising an immunogen, including TNFα conjugated to a carrier protein, including KLH (pp. 9 [corresponding to paragraphs 49 and 50 in the English translation]). The immunogenic complex of KLH and TNFα is taught using gluteraldehyde at p. 22 (see paragraph 134 of the English translation) (see also claims 1-4, 6, and 11).

Conclusion

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cherie M. Woodward whose telephone number is (571) 272-3329. The examiner can normally be reached on Monday - Thursday 9:00am-7:30pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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